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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 9/20, 9/50, 9/52</b> <b>A61K 31/19</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 91/15194</b> <b>(43) International Publication Date:</b> 17 October 1991 (17.10.91)
<b>(21) International Application Number:</b> PCT/US91/01089 <b>(22) International Filing Date:</b> 26 February 1991 (26.02.91) <b>(30) Priority data:</b> 508,193 11 April 1990 (11.04.90) US <b>(60) Parent Application or Grant</b> (63) Related by Continuation US 508,193 (CON) Filed on 11 April 1990 (11.04.90) <b>(71) Applicant (for all designated States except US):</b> THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).		<b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only) :</b> SHEN, Robert, Wu-Wei [US/US]; 5121 Maple Ridge Road, Kalamazoo, MI 49008 (US). <b>(74) Agent:</b> WILLIAMS, Sidney, B., Jr.; Corporate Patents & Trademarks, The Upjohn Company, Kalamazoo, MI 49001 (US). <b>(81) Designated States:</b> AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> TASTE MASKING OF IBUPROFEN BY FLUID BED COATING		
<b>(57) Abstract</b>  A chewable taste-masked ibuprofen tablet having controlled release characteristics.		

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TASTE MASKING OF IBUPROFEN BY FLUID BED COATINGBACKGROUND OF THE INVENTION

Ibuprofen is a well-known therapeutic agent. Its therapeutic activities include analgesia and anti-pyretic attack. As with most medicines, one of the difficulties with  
5 ibuprofen is in making it palatable to children. This difficulty has been overcome with most medicines by preparing formulations such as syrups and drops. The present invention relates to chewable tablets that are palatable to children and a process for making the tablets.

From a manufacturing cost standpoint, it is desirable to have chewable, taste-  
10 masked microcapsules that are large (0.25-1 mm in diameter), because larger microcapsules are easier to manufacture and package, and are less expensive to produce than are small microcapsules. However, an increase in size makes fracture during chewing and the release of drug from the microcapsule more likely to occur especially when there is an inadequate amount of plasticizer or other component included to provide  
15 elasticity. A larger sized microcapsule requires greater elasticity to minimize the likelihood that a fracture will occur and active agent will be released. There is therefore a need in the art of pharmaceutical formulation to provide encapsulating coatings capable of being formulated into chewable microcapsules as large as about 1.5 mm. that will not release drugs during chewing.

20 INFORMATION DISCLOSURE

Ibuprofen and its use for treatment of analgesia is disclosed in U.S. patent 3,385,886. Compositions containing ibuprofen and methods for using them are described in U.S. patent 3,228,831. New crystalline and high dose formulations of ibuprofen are disclosed in U.S. patents 4,476,248 and 4,609,675 respectively.

25 Microencapsulation is described by J.A. Bakan, Part Three of "The Theory and Practice of Industrial Pharmacy", 1986, pp. 413-429.

EUDRAGIT L30D is a known polymer useful for coating orally administered pharmaceutical dosage forms, particularly tablets, capsules and pills, with coatings which are resistant to gastric juices but solvent in intestinal juices.

30 Chewable taste-masked pharmaceutical compositions, including some containing ibuprofen, are described in U.S. patent 4,800,087. However, the compositions described therein require a coating consisting of a mixture of polymers. The use of fluidized bed for coating pharmaceutical products is described in U.S. Patent 4,800,087.

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### SUMMARY OF THE INVENTION

This invention involves:

A chewable taste-masked tablet having controlled release characteristics comprising a microcapsule of about 100 microns to about 0.8 mm in diameter having (a)  
5 a pharmaceutical core including crystalline ibuprofen and (b) a methacrylic acid copolymer coating having sufficient elasticity to withstand chewing.

While chewable taste masked formulations of ibuprofen are referred to in the prior art, among the advantages of the compositions of this invention over the closest prior art compositions is that the coating used consists of a single copolymer rather than  
10 a mixture of copolymers.

### DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises formulations of taste-masked microcapsules which further comprise (a) a pharmaceutical core of crystalline ibuprofen and (b) a methacrylic acid copolymer coating that may provide chewable taste-masked characteristics. Both the polymeric coating and the pharmaceutical core may further comprise  
15 diluents, fillers and other pharmaceutical additives which may effect the rate of release of active ibuprofen from the microcapsule.

The methacrylic acid copolymer is preferably dispersable in water so as to take advantage of aqueous formulation techniques and has a rapid rate of dissolution at a pH  
20 of about 5.5.. Aqueous-based coating systems are safe and make regulatory compliance (EPA) relatively easy compared to non-aqueous based coating systems. An elastic microcapsule which will not release ibuprofen in the mouth when chewed is contemplated by the present invention.

A preferred coating composition is a high temperature film forming polymer or  
25 "hard" polymer. A hard polymer is defined as a polymer that will form a film on a pharmaceutical core at a temperature of at least about 30°C. Examples of high temperature film forming polymers useful in this invention include hydroxypropylmethyl cellulose, for example, Pharmacoat' 606 brand from Shinetro Corp., Tokyo, Japan, hydroxypropyl cellulose, for example, Klucel' brand from Hercules Corp., Wilmington, Del., methylcellulose for example Methocel A', from Dow Chemical, Midland, Mich.,  
30 ethylcellulose, for example, Ethocel' brand from Dow Chemical Corp., and other aqueous polymeric dispersions such as Aquacost' Brand from FMC, Philadelphia, PA., and Surelease' brand from Colorcon, West Point, PA., polyvinyl alcohol, polyvinyl

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acetate, cellulose acetate butyrate, styrene acylate copolymers, for example Janocryl 138 (61°C. film forming copolymer from S.C. Johnson, Racine, Wis.) and copolymers of acrylic acid esters, for example, the EUDRAGIT Copolymers (Rohm Pharma GmbH, Westerstadt, W. Germany): Eudragit' L30D, Eudragit' L100-55, Eudragit' RS(30D and 100).

Eudragit' copolymers that are preferred in embodiments of this invention include L30D, an anionic copolymer based of polymethacrylic and acrylic acid esters (Methacrylic Acid Copolymer, Type C in USP XXII/NF XVI) with a mean molecular weight of 250,000.

The polymeric coating should provide for immediate release characteristics, i.e., rapid release of the active agents in the duodenum within a period of about one hour. When the microcapsules are formulated into chewable, taste-masked oral tablets or capsules, the formulations provide for immediate, rapid release in the stomach.

The chewable polymeric coating providing immediate release upon reaching the duodenum i.e., within one hour after ingestion may be comprised of a pharmaceutically compatible high temperature film forming polymer that is water insoluble or not swellable within the pH range (about 5.5-6.5) and/or the liquid content of the mouth and will not release the active agent in the mouth, but will dissolve or change in physical character in the duodenum, for example, swell or become more porous, thus releasing drug.

The most preferred film forming acrylic resin polymer that releases active agent rapidly in duodenum is EUDRAGIT L30D. EUDRAGIT L30D is a copolymer anionic in character, based on polymethacrylic acid and acrylic acid esters. Although EUDRAGIT L30D is soluble at pH's in the mouth and insoluble at pH's of the stomach, it has found usefulness in chewable, taste-masked immediate release formulations of the present invention. This usefulness may stem from the lack of liquid in the mouth, or may be the result of elastic qualities that EUDRAGIT L30D acquires when formulated in combination with a plasticizer, or preferably, with EUDRAGIT E30D.

Any of the above described high-temperature film-forming polymers may be used for microencapsulation. However, to make capsules of the required elasticity using the above described high temperature film forming polymers, plasticizers may be incorporated into the coatings. Plasticizers useful to provide the requisite elasticity include propylene glycol and polyalkylene glycols, for example, polyethylene glycol,

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triacetin, (glyceryl triacetate from Eastman Kodak, Rochester, NY vinyl pyrrolidone, diethyl phthallate, dibutylsebacate, and esters of citric acid among others. Generally, the plasticizers comprise between about 2% and about 50% by weight of polymer and plasticizer combined, preferably between about 5% and 15% by weight and most  
5 preferably about 10% by weight of the polymer and plasticizer combined.

The chewable tablets of this invention are prepared by spraying a solution of the methacrylic acid copolymer on to a fluidized bed of crystalline ibuprofen.

Crystalline ibuprofen can be prepared by the process described in U.S. Patent 4,476,248. The particle size of the ibuprofen should be about 80 to 500 microns and it  
10 it may contain excipients such as starch, lactose, hydroxypropyl methylcellulose, microcrystalline cellulose PVP, sucrose and fructose.

The residence time should be such that the ratio of copolymer to ibuprofen of each chewable tablet is about eight percent by weight.

The temperature of the inlet and outlet air should be maintained between 40 and  
15 60 C. 20 and 40 C. respectively. The preferred inlet and outlet air temperatures are between 45 and 55 and 33 and 27°C respectively.

The temperature of the fluidized bed should be maintained between 60 and 20, respectively. The preferred temperature of the bed is about 35 C.

The amount of ENDRAGIT L30D in the encapsulation formulation should be  
20 between about 10% to 60% by weight of ibuprofen, preferably about 14%.

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EMBODIMENT OF THE INVENTIONExample 1 Preparation of chewable ibuprofen tablet (#13, p 23)A. Encapsulated Ibuprofen

	Ibuprofen	4 Kg
5	Eudragit L30D	2.33 Kg (coating polymer)
	Propylene Glycol	140 gm (plasticizer)
	Talc	200 gm
	Purified Water	200 gm

Ibuprofen crystals (particle size #40-105) are air suspended in a closed chamber (Glatt GPCG5). An aqueous dispersion of Eudragit L 30D and talc is sprayed onto the fluidized bed of ibuprofen at a rate of 60gm/min. The inlet and outlet air temperature are maintained at 50°C. and 20-22°C. respectively. The air rate is adjusted so as to maintain the particles in a suspended state and to maintain the fluidized bed at a temperature of 35°C.

15 Air Atomizing Pressure 3.5 bar

B. Preparation of Chewable Tablets

		<u>Per Tab</u>	<u>Per 1000 Tab</u>
	Mannitol	5-44 mg	544 Gm
	Malic Acid	4 mg	4 Gm
20	Aspartame	12 mg	12 Gm
	Spray Dried Orange Flavor	18 mg	18 Gm
	Encapsulated Ibuprofen	127 mg	127 Gm
	Ac-Di-Sol	24 mg	24 Gm
25	Avicel pH102	60 mg	60 Gm
	F.D.C. Yellow 6 Lake	0.2 mg	0.2 Gm
	Citric Acid	4 mg	4 Gm
	Talc	20 mg	20 Gm

The compression mix of above was tabletted on a Manesty beta press with 1/2" flat face tooling. Tablet weight: 813 mg. Hardness: 9 - 13 Strong Cobert (SC). Disintegration Time in water: 2 minutes.

Table 1 shows a comparison of dissolution data between MOTRIN IB Tablet in PH 7.2 and the MOTRIN Chewable Tablets of this invention.

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Table 2 shows a comparison of dissolution data between MOTRIN IB Tablets in PH 5.8 and the MOTRIN Chewable Tablets of this invention.



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TABLE I

Comparison of Dissolution Data between Motrin IB  
and Motrin Chewable Tablets

5 Buffer 7.2 PH

	Motrin IB	#12	#13	Recrystallized Ibuprofen Raw Material
10	Flask 1	Flask 2	Flask 3	Flask 4
	Time % Released	Time % Released	Time % Released	Time % Released
	0.10 -0.02	0.20 0.00	0.30 0.04	0.40 -0.02
	2.10 1.21	2.20 10.50	2.30 9.40	2.40 0.48
15	4.10 38.77	4.20 63.24	4.30 53.61	4.40 18.34
	6.10 71.49	6.20 89.31	6.30 84.02	6.40 40.63
	8.10 84.88	8.20 97.65	8.30 89.89	8.40 54.00
	10.10 90.60	10.20 95.85	10.30 90.91	10.40 63.24
	12.10 92.79	12.20 93.61	12.30 91.45	12.40 71.12
20	14.10 93.80	14.20 91.77	14.30 91.45	14.40 78.23
	16.10 94.36	16.20 91.38	16.30 91.62	16.40 85.25
	18.10 94.58	18.20 91.64	18.30 91.66	18.40 87.75
	20.10 94.67	20.20 91.86	20.30 91.68	20.40 94.43
	22.10 94.75	22.20 91.88	22.30 91.77	22.40 96.05
25	24.10 94.77	24.20 92.01	24.30 91.79	24.40 99.24
	26.10 94.82	26.20 92.16	26.30 91.77	26.40 100.63
	28.10 94.88	28.20 92.40	28.30 91.79	28.40 101.32
	30.10 94.92	30.20 92.57	30.30 91.81	30.40 101.58
	32.10 94.95	32.20 92.79	32.30 91.88	32.40 101.71
30	34.10 95.01	34.20 92.83	34.30 91.90	34.40 102.14
	36.10 94.99	36.20 92.92	36.30 91.86	36.40 102.20
	38.10 95.03	38.20 92.96	38.30 91.86	38.40 102.35
	40.10 94.99	40.20 93.00	40.30 91.84	40.40 102.46
	42.10 95.05	42.20 93.09	42.30 91.90	42.40 102.61
35	44.10 95.10	44.20 93.15	44.30 91.92	44.40 102.66
	46.10 95.08	46.20 93.20	46.30 91.97	46.40 102.72
	48.10 95.10	48.20 93.24	48.30 91.97	48.40 102.74
	50.10 95.08	50.20 93.26	50.30 91.94	50.40 102.76
	52.10 95.14	52.20 93.26	52.30 91.94	52.40 102.79
40	54.10 95.12	54.20 93.33	54.30 92.01	54.40 102.79
	56.10 95.14	56.20 93.35	56.30 92.03	56.40 102.89
	58.10 95.18	58.20 93.37	58.30 92.05	58.40 102.85
	60.10 95.18	60.20 93.41	60.30 92.05	60.40 102.92

45 In PH7.2 buffer: Formula #12 shows fustic reline than Motrin IB.  
Formula #12, #13 and Motrin IB shows the same reline forte after 10 minutes.

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Formula #12, #13 all pass U.S.P. Tablets specification 20 minutes  
785%.

- 5      Flask 1: Motrin IB.  
      Flask 2: Motrin chewable experiment Lot 12.  
      Flask 3: Motrin chewable experiment Lot 13.  
      Flask 4: Recrystallized Ibuprofen.

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TABLE II

Buffer: 5-8 PH

5	Motrin IB	#12	#13	Recrystallized Ibuprofen Raw Material
	Flask 1	Flask 2	Flask 3	Flask 4
10	Time % Released	Time % Released	Time % Released	Time % Released
	0.10 0.04	0.20 0.02	0.30 0.00	0.40 0.04
	2.10 0.13	2.20 2.76	2.30 2.20	2.40 0.78
	4.10 2.25	4.20 9.78	4.30 7.90	4.40 9.18
	6.10 19.40	6.20 18.68	6.30 15.72	6.40 36.26
15	8.10 36.48	8.20 28.10	8.30 25.33	8.40 53.71
	10.10 48.08	10.20 36.05	10.30 34.69	10.40 65.90
	12.10 57.28	12.20 43.30	12.30 47.11	12.40 75.08
	14.10 64.34	14.20 51.49	14.30 56.54	14.40 82.38
	16.10 70.09	16.20 58.83	16.30 64.02	16.40 87.39
20	18.10 74.82	18.20 65.33	18.30 69.91	18.40 91.40
	20.10 78.57	20.20 71.02	20.30 74.86	20.40 94.41
	22.10 81.73	22.20 76.16	22.30 78.53	22.40 96.78
	24.10 84.47	24.20 80.43	24.30 81.51	24.40 98.47
	26.10 86.74	26.20 84.02	26.30 83.89	26.40 99.72
25	28.10 88.68	28.20 86.80	28.30 86.11	28.40 100.65
	30.10 90.24	30.20 89.05	30.30 87.78	30.40 101.51
	32.10 91.56	32.20 90.99	32.30 89.09	32.40 102.03
	34.10 92.70	34.20 92.53	34.30 90.06	34.40 102.53
	36.10 93.59	36.20 93.78	36.30 90.95	36.40 103.09
30	38.10 94.43	38.20 94.79	38.30 91.73	38.40 103.52
	40.10 95.21	40.20 95.62	40.30 92.46	40.40 103.91
	42.10 95.75	42.20 96.26	42.30 93.00	42.40 104.34
	44.10 96.29	44.20 96.76	44.30 93.50	44.40 104.67
	46.10 96.67	46.20 97.17	46.30 93.84	46.40 105.08
35	48.10 96.95	48.20 97.45	48.30 94.15	48.40 105.25
	50.10 97.21	50.20 97.65	50.30 94.36	50.40 105.46
	52.10 97.54	52.20 97.88	52.30 94.60	52.40 105.72
	54.10 97.75	54.20 98.12	54.30 94.77	54.40 105.94
	56.10 97.97	56.20 98.25	56.30 94.97	56.40 106.11
40	58.10 98.12	58.20 98.38	58.30 95.08	58.40 106.29
	60.10 98.27	60.20 98.47	60.30 95.18	60.40 106.37

PH 5-8:

After 10 minutes about 10-12% difference action compare #12, #13 with Motrin IB.

45

After 20 minutes about 7-8% difference when compared #12, and #13 with Motrin IB.

After 30 minutes shows no significant difference among them.

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- Flask 1: Motrin IB.
- Flask 2: Motrin chewable experiment Lot 12.
- Flask 3: Motrin chewable experiment Lot 13.
- Flask 4: Recrystallized Ibuprofen.

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CLAIMS

1. A chewable taste-masked tablet having controlled release characteristics comprising a microcapsule of about 100 microns to about 0.8 mm in diameter having (a)  
5 a pharmaceutical core including crystalline ibuprofen and (b) a methacrylic acid copolymer coating having sufficient elasticity to withstand chewing.
2. A chewable taste-masked pharmaceutical composition according to claim 1 wherein the copolymer is Eudragit L30D said coating being adapted to release said  
10 ibuprofen in the duodenum.
3. The composition according to claim 1, wherein said copolymer coating further comprises a plasticizer.
- 15 4. The composition according to claim 2, wherein said copolymer coating further comprises a plasticizer.
5. The composition according to claim 4, wherein said plasticizer is selected from the group consisting of glyceryl triacetate, triethyl citrate, acetyl triethyl citrate, dibutyl  
20 sebate, acetyl tributyl citrate, diethyl phthlate, dibutyl phthlate, glycerine, propylene glycol and polyethylene glycol.
6. The composition according to claim 5 wherein said plasticizer is propylene glycol.

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# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/01089

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC IPC <sup>5</sup> : A 61 K 9/20, 9/50, 9/52, 31/19														
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched <sup>7</sup></div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="padding: 5px;">IPC<sup>5</sup></td> <td style="padding: 5px;">A 61 K</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched <sup>8</sup></div>			Classification System	Classification Symbols	IPC <sup>5</sup>	A 61 K								
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IPC <sup>5</sup>	A 61 K													
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black;">Category <sup>9</sup></th> <th style="border-bottom: 1px solid black;">Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 15%; border-bottom: 1px solid black;">Relevant to Claim No. <sup>13</sup></th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">EP, A, 0212751 (FORMENTI) 4 March 1987 see claims 1-5, 9, 11, 13, 14, 21, 22; column 4, lines 33-47; column 5, lines 19-21 and 31; column 9, lines 1-6 --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-6</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">EP, A, 0212747 (PROCTER &amp; GAMBLE) 4 March 1987 see claims 1-3, 6, 7; page 5, lines 24-29 and 35; page 6, lines 1 and 16, 17; page 8, lines 28-29 --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-6</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">US, A, 4835186 (AMERICAN HOME) 30 May 1989 see claims 1, 2, 5; column 2, lines 31-33 and 40  -----</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-6</td> </tr> </table>			Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	Y	EP, A, 0212751 (FORMENTI) 4 March 1987 see claims 1-5, 9, 11, 13, 14, 21, 22; column 4, lines 33-47; column 5, lines 19-21 and 31; column 9, lines 1-6 --	1-6	Y	EP, A, 0212747 (PROCTER & GAMBLE) 4 March 1987 see claims 1-3, 6, 7; page 5, lines 24-29 and 35; page 6, lines 1 and 16, 17; page 8, lines 28-29 --	1-6	Y	US, A, 4835186 (AMERICAN HOME) 30 May 1989 see claims 1, 2, 5; column 2, lines 31-33 and 40  -----	1-6
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Y	US, A, 4835186 (AMERICAN HOME) 30 May 1989 see claims 1, 2, 5; column 2, lines 31-33 and 40  -----	1-6												
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>														
<b>IV. CERTIFICATION</b> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">           Date of the Actual Completion of the International Search            22nd May 1991         </td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;">           Date of Mailing of this International Search Report            11. 07. 91         </td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;">           International Searching Authority            EUROPEAN PATENT OFFICE         </td> <td style="border-bottom: 1px solid black; padding: 5px;">           Signature of Authorized Officer            F.W. HECK  </td> </tr> </table>			Date of the Actual Completion of the International Search 22nd May 1991	Date of Mailing of this International Search Report 11. 07. 91	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer F.W. HECK								
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		JP-A- 62111923	22-05-87
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